PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 218671	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US02/33243	International filing date *(day/month/year)* 15 October 2002 (15.10.2002)	Priority date *(day/month/year)*
International Patent Classification (IPC) or national classification and IPC IPC(7): A01N 63/00; C07H 21/02, 21/04; C12N 15/00, 15/63; C12P 21/06 and US Cl.: 424/93.2, 93.21; 435/69.1, 320.1, 455; 536/23.1, 23.5, 23.51		
Applicant THE GOVERNMENT OF UNITED STATES OF AMERICA		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of ___ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand 30 January 2004 (30.01.2004)	Date of completion of this report 01 February 2005 (01.02.2005)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Shin-Lin Chen Telephone No. 571-272-1600

Form PCT/IPEA/409 (cover sheet)(July 1998)

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I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-15 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 16-19, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the sequence listing part of the description:
pages 1-2, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

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IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:
   - ☐ restricted the claims.
   - ☒ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention is accordance with Rules 13.1, 13.2 and 13.3 is
   - ☐ complied with.
   - ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-14, drawn to a method of preparing autologous T-lymphocytes by obtaining PBMC from a patient immunized with an antigen of the cancer, stimulating the PBMC with said antigen in vitro, and tranducing said PBMC with a retroviral vector expressing human IL-2, and a composition comprising said autologous T lymophocyte.
Group II, claim(s) 15 and 16, drawn to a method of treating a patient having cancer with said autologous T lymphocytes.
Group III, claim(s) 17-30, drawn to a method of preparing autologous Tumor-infiltrating-lymphocytes (TIL) by obtaining TIL from a patient immunized with an antigen of the cancer, and tranducing said TIL with a retroviral vector expressing human IL-2, and a composition comprising said autologous TIL.
Group IV, claim(s) 31 and 32, drawn to a method of treating a patient having cancer with said autologous TIL.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The "special technical feature" shared by groups I-IV is transduction of T lymphocyte or TIL with a retroviral vector expressing IL-2 protein. Lupton et al., 1999 (US Patent No. 5,874,556) teaches introduction of a retroviral vector expressing stimulatory factor, such as IL-2, into an activated lymphocyte, such as CD8+ CTL, wherein expression of the IL-2 protein in lymphocyte can reduce dependency of the lymphocyte on T helper cells for proliferation (e.g. column 43, 44). Li et al., 1999 (Zhongguo Mianyixue Zazhi, Vol. 15, p. 331-332) reports transduction of TIL from hepatocellular carcinoma with vector SV-IL2 expressing IL-2 protein and the transduced TIL secret higher level of IL-2 as compared to untransduced TIL (abstract). Thus, no "special technical feature" has been contributed by the present invention over the prior art. Therefore, Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1.

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
   - ☒ all parts.
   - ☐ the parts relating to claims Nos. ____

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V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-32	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 1-32	YES
	Claims NONE	NO
Industrial Applicability (IA)	Claims 1-32	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-32 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest stimulating the PBMCs, obtained from a patient immunized with an antigen of a cancer, with the antigen of the cancer in vitro.

Claims 1-32 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject mattter claimed can be made or used in industry.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 15, 16, 31 and 32 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because of the claims are not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because: the claims are directed to a method of treating a patient with cancer by administering to the patient autologous T lymphocytes or autologous TILs. The art of using immunized and genetically modified cells in treating cancer in vivo was unpredictable at the time of the invention. It is unclear whether the T lymphocytes or TILs can produce and secret sufficient IL-2 and antibody against cancer antigen so as to achieve therapeutic effects in vivo. Further, administration routes of the T lymphocytes or TILs also paly important roles in determining whether sufficient T lymphocytes or TILs can reach target cancer cells, and whether sufficient IL-2 and antibody against cancer antigen can be present at target cancer cells so as to achieve therapeutic effects in vivo.